Exhibit 1

1: Tissue Eng. 2006 Jul 1; [Epub ahead of print]

Human Mesenchymal Stem Cells Induce T Cell Anergy and Downregulate T Cell Allo-Responses via the TH2 Pathway: Relevance to Tissue Engineering Human Heart Valves.

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To generate an "off the shelf" tissue-engineered heart valve, the cells would need to be of allogeneic origin. Here, we report the possibility of using human bone marrow-derived mesenchymal stem cells (MSCs) as a suitable allogeneic cell source for tissue-engineered heart valves. Proliferative responses of primary and primed CD4(+) T cells to allogeneic MSCs were examined. A protein microarray system was used to detect soluble factors from supernatants collected from the T cell assays. MSCs are poor stimulators of primary and primed CD4(+) T cell proliferation, despite provision of B7-1 trans- co-stimulation. MSCs not only directly inhibited primary and primed T cell responses to allogeneic peripheral blood mononuclear cells (PBMCs), but 24-h pre-culture of T cells with MSCs suppressed subsequent T cell proliferative responses to allogeneic PBMCs in a contact-dependent manner. Analysis of supernatants revealed a distinctly different cytokine profile after co-culture of T cells with MSCs than with PBMCs or endothelial cells. Pro-inflammatory Th1 cytokines interleukin (IL)-1alpha and beta, interferon (IFN) gamma, and tumor necrosis factor (TNF)alpha were downregulated, whereas, anti-inflammatory Th2 cytokines IL-3, IL-5, IL-10, and IL-13 and the Th2 chemokine I-309, a chemoattractant for regulatory T cells, were upregulated. Further analysis revealed that after co-culture with MSCs, the T cells exhibited a regulatory phenotype (CD4(+)CD25(lo) CD69(lo)FoxP3(+)). MSCs downregulate T cell responses through direct contact and secretion of anti-inflammatory and tolerogenic cytokines, which may involve the recruitment of regulatory T cells. This implies that allogeneic MSCs could be a suitable cell source for tissue engineering a heart valve.

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